

SEQUENCE LISTING

<110> Holmes, Stephen D.
Ho, Yen Sen
Taylor, Alexander
Abdel-Meguid, Sherin S.

<120> Recombinant IL-18 Antagonists Useful in Treatment of IL-18 Mediated Disorders

<130> P50897

<140> 60/125,299

<141> 1999-03-19

<160> 48

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gaa act gtc tcc atc gaa tgt ctg gca agt gag gac ata tac act tat 96
Glu Thr Val Ser Ile Glu Cys Leu Ala Ser Glu Asp Ile Tyr Thr Tyr
20 25 30

tta aca tgg tat cag cag aaa cca ggg aaa tct cct caa ctc ctg atc 144
 Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
 35 40 45

tat ggt gca aat aag ttg caa gat ggg gtc cca tca cgg ttc agt ggc 192
 Tyr Gly Ala Asn Lys Leu Gln Asp Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

agt gga tct ggc aca cag tat tct ctc aag atc agc ggc ata caa cct 240
 Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Ser Gly Ile Gln Pro
 65 70 75 80

gaa gat gaa ggg gat tat ttc tgt cta cag ggt tcc aag ttt ccg ctc 288
 Glu Asp Glu Gly Asp Tyr Phe Cys Leu Gln Gly Ser Lys Phe Pro Leu
 85 90 95

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<210> 2

<211> 108

<212> PRT

<213> Rattus norvegicus

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 20 25 30
 Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
 35 40 45
 Tyr Gly Ala Asn Lys Leu Gln Asp Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Ser Gly Ile Gln Pro
 65 70 75 80
 Glu Asp Glu Gly Asp Tyr Phe Cys Leu Gln Gly Ser Lys Phe Pro Leu
 85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg
 100 105

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<220>
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 <223> VK2C10 Light Chain CDR I

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 <211> 11
 <212> PRT
 <213> Rattus norvegicus

<400> 4
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<212> PRT
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<400> 6
Gly Ala Asn Lys Leu Gln Asp
1 5

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<400> 8
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tct gtg aag tta tct tgc aaa gtt tct ggc gaa ata agt aca gga tac	96
Ser Val Lys Leu Ser Cys Lys Val Ser Gly Glu Ile Ser Thr Gly Tyr	
20 25 30	

tat ttc cac ttt gtg agg cga agg cct gga cag ggt ctg gaa tgg ata	144
Tyr Phe His Phe Val Arg Arg Arg Pro Gly Gln Gly Leu Glu Trp Ile	
35 40 45	

gga agg att gat cct gag gat gat agt act aaa tat gct gag agg ttc	192
Gly Arg Ile Asp Pro Glu Asp Asp Ser Thr Lys Tyr Ala Glu Arg Phe	
50 55 60	

aaa gac agg gcg acg ctc act gca caa aca tcc tcc aac aca gcc tac	240
Lys Asp Arg Ala Thr Leu Thr Ala Gln Thr Ser Ser Asn Thr Ala Tyr	
65 70 75 80	

ctg aac ctc agc agc ctg acc tct gag gac act gca act tat ttt tgt	288
Leu Asn Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Thr Tyr Phe Cys	
85 90 95	

acc aca tgg cgg ata tac cga gat agt tct ggc cgc ccc ttc tat gtt	336
Thr Thr Trp Arg Ile Tyr Arg Asp Ser Ser Gly Arg Pro Phe Tyr Val	
100 105 110	

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<212> PRT

<213> Rattus norvegicus

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 20 25 30
 Tyr Phe His Phe Val Arg Arg Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45
 Gly Arg Ile Asp Pro Glu Asp Asp Ser Thr Lys Tyr Ala Glu Arg Phe
 50 55 60
 Lys Asp Arg Ala Thr Leu Thr Ala Gln Thr Ser Ser Asn Thr Ala Tyr
 65 70 75 80
 Leu Asn Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Thr Tyr Phe Cys
 85 90 95
 Thr Thr Trp Arg Ile Tyr Arg Asp Ser Ser Gly Arg Pro Phe Tyr Val
 100 105 110
 Met Asp Ala Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser
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<210> 11

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<212> DNA

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<223> VH2C10 Heavy chain CDR I

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Gly Tyr Tyr Phe His

1

5

15

<210> 12

<211> 5

<212> PRT

<213> Rattus norvegicus

<400> 12

Gly Tyr Tyr Phe His

1 5

<210> 13

<211> 51

<212> DNA

<213> Rattus norvegicus

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<222> (1)...(51)

<223> VH2C10 Heavy chain CDR II

<400> 13

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gac 51

<210> 14

<211> 16

<212> PRT

<213> Rattus norvegicus

<400> 14

Arg Ile Asp Pro Glu Asp Asp Ser Thr Lys Tyr Ala Glu Arg Phe Lys
1 5 10 15

<210> 15

<211> 51

<212> DNA

<213> Rattus norvegicus

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<222> (1)...(51)

<223> VH2C10 Heavy chain CDR III

<400> 15

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gcc 51

<210> 16

<211> 16

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<213> Rattus norvegicus

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Trp Arg Ile Tyr Arg Asp Ser Ser Gly Arg Pro Phe Tyr Val Met Asp
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<211> 342

<212> DNA

<213> Mus musculus

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<221> CDS

<222> (1)...(342)

<223> Light chain V region

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gat caa gcc tcc atc tct tgc aga tct agt cag agc ctt gta cac agt 96
 Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
 20 25 30

aat gga aac acc tat tta cat tgg tac ctg cag aag cca ggc cag tct 144
 Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

cca aag ctc ctg atc tac aaa gtt tcc aac cga ttt tct ggg gtc cca 192
 Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

gac agg ttc agt ggc agt gga tca ggt aca gat ttc aca ctc aag atc 240
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 agc aga gtg gag gct gag gat ctg gga gtt tat ttc tgc tct caa agt 288
 Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
 85 90 95
 aca cat gtt cct ccg tac acg ttc gga ggg ggg acc aag ctg gaa ata 336
 Thr His Val Pro Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
 100 105 110
 aaa cgg 342
 Lys Arg

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 <212> PRT
 <213> Mus musculus

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 35 40 45
 Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
 85 90 95
 Thr His Val Pro Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
 100 105 110
 Lys Arg

<210> 19
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<212> DNA

<213> Mus musculus

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<223> VK13G9 Light Chain CDR I

<400> 19

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aga tct agt cag agc ctt gta cac agt aat gga aac acc tat tta cat      48
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 1              5              10              15

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<210> 20

<211> 16

<212> PRT

<213> Mus musculus

<400> 20

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 1              5              10              15

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<223> VK13G9 Light chain CDR II

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<212> PRT

<213> Mus musculus

<400> 22

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1

5

<210> 23

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<212> DNA

<213> Mus musculus

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<221> CDS

<222> (1)...(30)

<223> CK13G9 Light chain CDR III

<400> 23

tct caa agt aca cat gtt cct ccg tac acg

30

Ser Gln Ser Thr His Val Pro Pro Tyr Thr

1

5

10

<210> 24

<211> 10

<212> PRT

<213> Mus musculus

<400> 24

Ser Gln Ser Thr His Val Pro Pro Tyr Thr

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5

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<212> DNA

<213> Mus musculus

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<221> CDS

<222> (1)...(369)

<223> Heavy chain V region

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acc ctc agt ctg act tgt tct ttc tct ggg ttt tct ctg agc act tct 96
 Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
 20 25 30

ggc atg ggt att gcc tgg gtt cgt cag cct tca ggg aag ggt ctg gag 144
 Gly Met Gly Ile Ala Trp Val Arg Gln Pro Ser Gly Lys Gly Leu Glu
 35 40 45

tgg ctg gca gac att tgg tgg gat gat aat aag tat tat aat cca tcc 192
 Trp Leu Ala Asp Ile Trp Trp Asp Asp Asn Lys Tyr Tyr Asn Pro Ser
 50 55 60

ctg gag agc cag ctc aca atc tcc aag gat acc tcc aga aac cag gta 240
 Leu Glu Ser Gln Leu Thr Ile Ser Lys Asp Thr Ser Arg Asn Gln Val
 65 70 75 80

ttc ctc acg atc acc agt gtg gac act gca gat tct gcc act tat tac 288
 Phe Leu Thr Ile Thr Ser Val Asp Thr Ala Asp Ser Ala Thr Tyr Tyr
 85 90 95

tgt gct cgt cat cat tac gac ggt agt agc ctc ctg cct atg gac tac 336
 Cys Ala Arg His His Tyr Asp Gly Ser Ser Leu Leu Pro Met Asp Tyr
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tgg ggt caa gga acc tca gtc acc gtc tcc tca 369
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<210> 26

<211> 123

<212> PRT

<213> Mus musculus

<400> 26

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<213> Mus musculus

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<221> CDS

<222> (1)...(48)

<223> VH13G9 Heavy chain CDR II

<400> 29

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<210> 30

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<212> PRT

<213> Mus musculus

<400> 30

Asp Ile Trp Trp Asp Asp Asn Lys Tyr Tyr Asn Pro Ser Leu Glu Ser
 1 5 10 15

<210> 31

<211> 39

<212> DNA

<213> Mus musculus

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<223> VH13G9 Heavy chain CDR III

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<210> 32

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<212> PRT

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<210> 33

<211> 324

<212> DNA

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<222> (1)...(324)

<223> Light chain V region

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 1 5 10 15

gaa act gtc tcc atc gaa tgt cta gca agt gag gac ata tac agt tat 96
 Glu Thr Val Ser Ile Glu Cys Leu Ala Ser Glu Asp Ile Tyr Ser Tyr
 20 25 30

tta gca tgg tat caa cag aag cca ggg aaa tct cct cag ctc ctg atc 144
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
 35 40 45

tat gcc aca aaa agg ttg caa gat ggg gtc cca tca cgg ttc agt ggc 192
 Tyr Ala Thr Lys Arg Leu Gln Asp Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

agt gga tct ggc aca cag tat tct ctc aaa ata agc gac atg caa cct 240
 Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Ser Asp Met Gln Pro
 65 70 75 80

gaa gat gaa ggg gat tat ttc tgt cta cag aat tcc aag ttt ccg gtc 288
 Glu Asp Glu Gly Asp Tyr Phe Cys Leu Gln Asn Ser Lys Phe Pro Val
 85 90 95

acg ttc ggt tct ggg acc aag ctg gag atc aaa cgg 324
 Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg
 100 105

15/21

<210> 34
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 35 40 45
 Tyr Ala Thr Lys Arg Leu Gln Asp Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Ser Asp Met Gln Pro
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 Glu Asp Glu Gly Asp Tyr Phe Cys Leu Gln Asn Ser Lys Phe Pro Val
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 Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg
 100 105

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 <223> VK14B7 Light chain CDR I

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<400> 36

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<210> 37

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<212> DNA

<213> Rattus norvegicus

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<223> CK14B7 Light chain CDR II

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<210> 38

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<212> PRT

<213> Rattus norvegicus

<400> 38

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<213> Rattus norvegicus

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<221> CDS

<222> (1)...(27)

<223> VK14B7 Light chain CDR III

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<213> Rattus norvegicus

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<210> 41

<211> 368

<212> DNA

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<222> (1)...(368)

<223> Heavy chain V region

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1

5

10

15

tct gtg aag ttt tct tgc aaa gtt tct ggc gat acc cct aca aca tac 96

Ser Val Lys Phe Ser Cys Lys Val Ser Gly Asp Thr Pro Thr Thr Tyr

20

25

30

tac gtg cac ttt gtg aga caa agg cct gga cag ggt ctg gaa tgg ata 144

Tyr Val His Phe Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile

35

40

45

gga agg att gat cct gag gat act agt act aaa tat gct gag aag ttc 192

Gly Arg Ile Asp Pro Glu Asp Thr Ser Thr Lys Tyr Ala Glu Lys Phe

50

55

60

aga aat aag gcg aca ttc act gca gat cca tcc tcc aac aca gcc tac 240

Arg Asn Lys Ala Thr Phe Thr Ala Asp Pro Ser Ser Asn Thr Ala Tyr
 65 70 75 80

cta aac ctc agc agc ctg acc cct gag gac act gca acc tat ttt tgt 288
 Leu Asn Leu Ser Ser Leu Thr Pro Glu Asp Thr Ala Thr Tyr Phe Cys
 85 90 95

acc ata atg cgg tac cat agt acc tat agg gtc tat gtt atg gat ttc 336
 Thr Ile Met Arg Tyr His Ser Thr Tyr Arg Val Tyr Val Met Asp Phe
 100 105 110

tgg ggt caa gga act gca gtc act gtc tcc tc 368
 Trp Gly Gln Gly Thr Ala Val Thr Val Ser
 115 120

<210> 42

<211> 122

<212> PRT

<213> Rattus norvegicus

<400> 42

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 20 25 30
 Tyr Val His Phe Val Arg Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45
 Gly Arg Ile Asp Pro Glu Asp Thr Ser Thr Lys Tyr Ala Glu Lys Phe
 50 55 60
 Arg Asn Lys Ala Thr Phe Thr Ala Asp Pro Ser Ser Asn Thr Ala Tyr
 65 70 75 80
 Leu Asn Leu Ser Ser Leu Thr Pro Glu Asp Thr Ala Thr Tyr Phe Cys
 85 90 95
 Thr Ile Met Arg Tyr His Ser Thr Tyr Arg Val Tyr Val Met Asp Phe
 100 105 110
 Trp Gly Gln Gly Thr Ala Val Thr Val Ser
 115 120

<210> 43

<211> 15

<212> DNA

<213> Rattus norvegicus

<220>

<221> CDS

<222> (1)...(15)

<223> VH14B7 Heavy chain CDR I

<400> 43

aca tac tac gtg cac

15

Thr Tyr Tyr Val His

1

5

<210> 44

<211> 5

<212> PRT

<213> Rattus norvegicus

<400> 44

Thr Tyr Tyr Val His

1

5

<210> 45

<211> 51

<212> DNA

<213> Rattus norvegicus

<220>

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<222> (1)...(51)

<223> VH14B7 Heavy chain CDR II

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48

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aat

51

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<400> 46

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1 5 10 15

<210> 47

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<212> DNA

<213> Rattus norvegicus

<220>

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<222> (1)...(42)

<223> VH14B7 Heavy chain CDR III

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1 5 10

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<210> 48

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<212> PRT

<213> Rattus norvegicus

<400> 48

Met Arg Tyr His Ser Thr Tyr Arg Val Tyr Val Met Asp Phe
1 5 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07349

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07 K 16/18; A61 K 39/395; C12 N 5/12, 15/12

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/388.1, 388.23; 435/326; 536/23.5; 424/130.1, 139.1, 141.1, 142.1, 145.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

West, US Patent full, STN via medline, caplus, embase, biosis. Search terms, interleukin-18 or IL-18, antibodies, monoclonal, humanized, 2C10, 14B7, 13G9

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REKVIG et al. Molecular analyses of anti-DNA antibodies induced by polymavirus BK in Balb/c mice. Scandinavian Journal of Immunology. 1995, Vol.41, No.6, pages 593-602. See sequence comparison "A".	14
X	BONILLA et al. V kappa gene usage, idiotype expression and antigen binding among clones expressing the VHX24 gene family derived from naive and anti-idiotype immune Balb/c mice. Journal of Immunolgy. 15 July 1990, Vol.145, No.2, pages 616-622, see sequence comparison "B"	14

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

29 JUNE 2000

Date of mailing of the international search report

04 AUG 2000

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07349

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JONES et al. Expression of TIMP3 mRNA is elevated in retinas affected by simplex retinitis pigmentosa. FEBS Letters. October 1994, Vol.352, No.2, pages 171-174, see sequence comparison "C"	15
X	EP 0528767 A1 (SANDOZ, LTD.) 24 February 1993 (24.02.93), see page 35, also see sequence comparison "D"	14
A, P	EP 0974600 A2 (KABUSHIKI KAISHA HAYASHIBARA SEIBUTSU KASAKU KENKYUJO) 26 January 2000 (26.01.2000), see entire document.	1-26
A	WO 99/09063 A1 (VEDA RESEARCH AND DEVELOPMENT CO. LTD.) 25 February 1999 (25.02.99), see entire document.	1-26

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/07349

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

530/388.1, 388.23; 435/326; 536/23.5; 424/130.1, 139.1, 141.1, 142.1, 145.1

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-4, 7-8, 11-26, drawn to a rat monoclonal antibody (Rat 2C10) specific for human IL-18, a hybridoma cell line producing said antibody a nucleic acid encoding said antibody, a pharmaceutical composition comprising said antibody, a method of treatment using said antibody and a method of diagnosis using said antibody.

Group II, claims 1-3, 5, 7, 9, 11-26, drawn to a rat monoclonal antibody (Murine 13G9) specific for human IL-18, a hybridoma cell line producing said antibody a nucleic acid encoding said antibody, a pharmaceutical composition comprising said antibody, a method of treatment using said antibody and a method of diagnosis using said antibody.

Group III, claims 1-3, 6-7, 10-26, drawn to a rat monoclonal antibody (Rat 14B7) specific for human IL-18, a hybridoma cell line producing said antibody a nucleic acid encoding said antibody, a pharmaceutical composition comprising said antibody, a method of treatment using said antibody and a method of diagnosis using said antibody.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Pursuant to 37 C.F.R § 1.475 (d), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly, the main invention (Group I) comprises the first-recited product, the Rat 2C10 antibody and the nucleic acid molecule encoding it, a method of using it. Further pursuant to 37 C.F.R § 1.475 (d), the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and

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methods accordingly defines a separate invention.